

1. NAME OF THE MEDICINAL PRODUCT

Forxiga 5 mg film-coated tablets
Forxiga 10 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Forxiga 5 mg film-coated tablets :
Each tablet contains dapagliflozin propanediol monohydrate equivalent to 5 mg dapagliflozin.

Excipient with known effect:

Each tablet contains 25 mg of lactose anhydrous.

Forxiga 10 mg film-coated tablets:

Each tablet contains dapagliflozin propanediol monohydrate equivalent to 10 mg dapagliflozin.

Excipient with known effect:

Each tablet contains 50 mg of lactose anhydrous.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Forxiga 5 mg film-coated tablets

Yellow, biconvex, 0.7 cm diameter round, film-coated tablets with “5” engraved on one side and “1427” engraved on the other side.

Forxiga 10 mg film-coated tablets

Yellow, biconvex, approximately 1.1 x 0.8 cm diagonally diamond-shaped, film-coated tablets with “10” engraved on one side and “1428” engraved on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Forxiga is indicated

in adults aged 18 years and older for the treatment of insufficiently controlled type 2 diabetes mellitus as an adjunct to diet and exercise

- as monotherapy when metformin is considered inappropriate due to intolerance.
- in addition to other medicinal products for the treatment of type 2 diabetes.

For study results with respect to combination of therapies, effects on glycaemic control and cardiovascular events, and the populations studied, see sections 4.4, 4.5 and 5.1.

to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure (NYHA class II-IV) with reduced ejection fraction.

to reduce the risk of sustained eGFR decline, end-stage kidney disease, cardiovascular death, and hospitalization for heart failure in adults with chronic kidney disease at risk of progression.

Limitations of Use

- FORXIGA is not recommended for the treatment of chronic kidney disease in patients with polycystic kidney disease or patients requiring or with a recent history of immunosuppressive therapy for kidney disease. FORXIGA is not expected to be effective in these populations.

4.2 Posology and method of administration

Prior to initiation of Forxiga

Assess renal function prior to initiation of FORXIGA therapy and then as clinically indicated [see Warnings and Precautions].

Assess volume status and, if necessary, correct volume depletion prior to initiation of FORXIGA [see Warnings and Precautions]

Posology

Type 2 Diabetes Mellitus

When dapagliflozin is used to treat T2DM in combination with insulin or an insulin secretagogue, such as a sulphonylurea, a lower dose of insulin or insulin secretagogue may be considered to reduce the risk of hypoglycaemia (see sections 4.5 and 4.8).

See Table 1 for dosage recommendations based on estimated glomerular filtration rate (eGFR).

Table 1. Recommended Dosage

eGFR (mL/min/1.73 m ²)	Recommended Dose
eGFR 45 or greater	For all indications, the recommended starting dose is 10 mg orally once daily.
eGFR 25 to less than 45	For the treatment of insufficiently controlled type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m ² , Forxiga is not recommended* . For all other indications, the recommended starting dose is 10 mg orally once daily.
eGFR less than 25	Initiation is not recommended, however patients may continue 10 mg orally once daily to reduce the risk of eGFR decline, ESKD, CV death and hHF.
On dialysis	Contraindicated.

* *FORXIGA is not recommended for the treatment of insufficiently controlled type 2 diabetes mellitus with an eGFR less than 45 mL/min/1.73 m². FORXIGA is likely to be ineffective in this setting based upon its mechanism of action.*

hHF: hospitalization for heart failure, CV: Cardiovascular, ESKD: End Stage Kidney Disease.

Hepatic impairment

No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg (see sections 4.4 and 5.2).

Elderly (≥ 65 years)

No dosage adjustment is recommended based on age.

Paediatric population

The safety and efficacy of dapagliflozin in children aged 0 to < 18 years have not yet been established. No data are available.

Method of administration

Forxiga can be taken orally once daily at any time of day with or without food. Tablets are to be swallowed whole.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Patients on dialysis

4.4 Special warnings and precautions for use

Hepatic impairment

There is limited experience in clinical studies in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment (see sections 4.2 and 5.2).

Use in patients at risk for volume depletion and/or hypotension

Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies (see section 5.1). It may be more pronounced in patients with very high blood glucose concentrations.

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected (see section 4.8).

Ketoacidosis in Patients with Diabetes Mellitus

Reports of ketoacidosis, including life-threatening and fatal cases, have been identified in post marketing surveillance in patients with type 1 and type 2 diabetes mellitus receiving sodium glucose co-transporter-2 (SGLT2) inhibitors, including FORXIGA. In placebo-controlled trials of patients with type 1 diabetes mellitus, the risk of ketoacidosis was increased in patients who received SGLT2 inhibitors compared to patients who received placebo. .

The reports were seen in patients treated with type 2 diabetes and type 1 diabetes. FORXIGA is not indicated for the treatment of patients with type 1 diabetes mellitus. It may increase the risk of diabetic ketoacidosis in these patients.

In a number of cases, the presentation of the condition was atypical with only moderately increased blood (Relative to expectations in diabetic ketoacidosis) glucose values, below 14 mmol/l (250 mg/dl), therefore the ketoacidosis wasn't immediately identified, and treatment was delayed.

DKA risk factors includes: Insulin dose reduction, acute febrile illness, reduced caloric intake due to illness or surgery, dehydration, pancreatic disorders suggesting insulin deficiency (e.g., type 1 diabetes, history of pancreatitis or pancreatic surgery), and alcohol abuse. The patients Risk factors should be assessed and taken into consideration before beginning treatment with FORXIGA.

You should monitor DKA and consider a temporary interruption of treatment in situation that raise the risk of developing DKA, such as: hospitalization for major surgical procedures or acute serious medical illnesses.

Patients should be alerted to symptoms and signs of DKA, including: nausea, vomiting, abdominal pain, fatigue, difficulty breathing, lack of appetite, confusion, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat.

Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level (even if their blood glucose levels are less than 250 mg/dL).

If ketoacidosis is suspected, FORXIGA should be discontinued, the patient should be evaluated and prompt treatment should be instituted.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Post-marketing cases of necrotising fasciitis of the perineum (also known as Fournier's gangrene) have been reported in female and male patients taking SGLT2 inhibitors (see section 4.8). This is a rare but serious and potentially life-threatening event that requires urgent surgical intervention and antibiotic treatment.

Patients should be advised to seek medical attention if they experience a combination of symptoms of pain, tenderness, erythema, or swelling in the genital or perineal area, with fever or malaise. Be aware that either uro-genital infection or perineal abscess may precede necrotising fasciitis. If Fournier's gangrene is suspected, Forxiga should be discontinued and prompt treatment (including antibiotics and surgical debridement) should be instituted.

Urinary tract infections

Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of dapagliflozin should be considered when treating pyelonephritis, urosepsis

Elderly (≥ 65 years)

Elderly patients may be at a greater risk for volume depletion and are more likely to be treated with diuretics.

Elderly patients are more likely to have impaired renal function, and/or to be treated with anti-hypertensive medicinal products that may cause changes in renal function such as angiotensin-converting enzyme inhibitors (ACE-I) and angiotensin II type 1 receptor blockers (ARB). The same recommendations for renal function apply to elderly patients as to all patients (see sections 4.2, 4.4, 4.8 and 5.1).

Cardiac failure

Experience with dapagliflozin in NYHA class IV is limited.

Chronic kidney disease

There is no experience with dapagliflozin for the treatment of chronic kidney disease in patients without diabetes who do not have albuminuria. Patients with albuminuria may benefit more from treatment with dapagliflozin.

Lower limb amputations

An increase in cases of lower limb amputation (primarily of the toe) has been observed in long-term, clinical studies in type 2 diabetes mellitus with SGLT2 inhibitors. It is unknown whether this constitutes a class effect. It is important to counsel patients with diabetes on routine preventative foot care.

Urine laboratory assessments

Due to its mechanism of action, patients taking Forxiga will test positive for glucose in their urine.

Lactose

The tablets contain lactose anhydrous. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacodynamic interactions

Diuretics

Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension (see section 4.4).

Insulin and insulin secretagogues

Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin (see sections 4.2 and 4.8).

Pharmacokinetic interactions

The metabolism of dapagliflozin is primarily via glucuronide conjugation mediated by UDP glucuronosyltransferase 1A9 (UGT1A9).

In *in vitro* studies, dapagliflozin neither inhibited cytochrome P450 (CYP) 1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, nor induced CYP1A2, CYP2B6 or CYP3A4. Therefore, dapagliflozin is not expected to alter the metabolic clearance of co-administered medicinal products that are metabolised by these enzymes.

Effect of other medicinal products on dapagliflozin

Interaction studies conducted in healthy subjects, using mainly a single dose design, suggest that the pharmacokinetics of dapagliflozin are not altered by metformin, pioglitazone, sitagliptin, glimepiride, voglibose, hydrochlorothiazide, bumetanide, valsartan, or simvastatin.

Following coadministration of dapagliflozin with rifampicin (an inducer of various active transporters and drug-metabolising enzymes) a 22% decrease in dapagliflozin systemic exposure (AUC) was observed, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended. A clinically relevant effect with other inducers (e.g. carbamazepine, phenytoin, phenobarbital) is not expected.

Following coadministration of dapagliflozin with mefenamic acid (an inhibitor of UGT1A9), a 55% increase in dapagliflozin systemic exposure was seen, but with no clinically meaningful effect on 24-hour urinary glucose excretion. No dose adjustment is recommended.

Effect of dapagliflozin on other medicinal products

In interaction studies conducted in healthy subjects, using mainly a single-dose design, dapagliflozin did not alter the pharmacokinetics of metformin, pioglitazone, sitagliptin, glimepiride, hydrochlorothiazide, bumetanide, valsartan, digoxin (a P-gp substrate) or warfarin (S-warfarin, a CYP2C9 substrate), or the anticoagulatory effects of warfarin as measured by INR. Combination of a single dose of dapagliflozin 20 mg and simvastatin (a CYP3A4 substrate) resulted in a 19% increase in AUC of simvastatin and 31% increase in AUC of simvastatin acid. The increase in simvastatin and simvastatin acid exposures are not considered clinically relevant.

Interference with 1,5-anhydroglucitol (1,5-AG) Assay

Monitoring glycaemic control with 1,5-AG assay is not recommended as measurements of 1,5AG are unreliable in assessing glycaemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycaemic control.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of dapagliflozin in pregnant women. Studies in rats have shown toxicity to the developing kidney in the time period corresponding to the second and third trimesters of human pregnancy (see section 5.3). Therefore, the use of dapagliflozin is not recommended during the second and third trimesters of pregnancy.

When pregnancy is detected, treatment with dapagliflozin should be discontinued.

Breast-feeding

It is unknown whether dapagliflozin and/or its metabolites are excreted in human milk. Available pharmacodynamic/toxicological data in animals have shown excretion of dapagliflozin/metabolites in milk, as well as pharmacologically-mediated effects in nursing offspring (see section 5.3). A risk to the newborns/infants cannot be excluded. Dapagliflozin should not be used while breast-feeding.

Fertility

The effect of dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested.

4.7 Effects on ability to drive and use machines

Forxiga has no or negligible influence on the ability to drive and use machines. Patients should be alerted to the risk of hypoglycaemia when dapagliflozin is used in combination with a sulphonylurea or insulin.

4.8 Undesirable effects

Summary of the safety profile

Type 2 diabetes mellitus

In the clinical studies in type 2 diabetes, more than 15,000 patients have been treated with dapagliflozin.

The primary assessment of safety and tolerability was conducted in a pre-specified pooled analysis of 13 short-term (up to 24 weeks) placebo-controlled studies with 2,360 subjects treated with dapagliflozin 10 mg and 2,295 treated with placebo.

In the dapagliflozin cardiovascular outcomes study in type 2 diabetes mellitus (DECLARE study, see section 5.1), 8,574 patients received dapagliflozin 10 mg and 8,569 received placebo for a median exposure time of 48 months. In total, there were 30,623 patient-years of exposure to dapagliflozin.

The most frequently reported adverse reactions across the clinical studies were genital infections.

Heart failure

In the dapagliflozin cardiovascular outcome study in patients with heart failure with reduced ejection fraction (DAPA-HF study), 2,368 patients were treated with dapagliflozin 10 mg and 2,368 patients with placebo for a median exposure time of 18 months. The patient population included

patients with type 2 diabetes mellitus and without diabetes, and patients with eGFR \geq 30 mL/min/1.73 m².

The overall safety profile of dapagliflozin in patients with heart failure was consistent with the known safety profile of dapagliflozin.

Chronic kidney disease

In the dapagliflozin renal outcome study in patients with chronic kidney disease (DAPA-CKD), 2,149 patients were treated with dapagliflozin 10 mg and 2,149 patients with placebo for a median exposure time of 27 months. The patient population included patients with type 2 diabetes mellitus and without diabetes, with eGFR \geq 25 to \leq 75 mL/min/1.73 m², and albuminuria (urine albumin creatinine ratio [UACR] \geq 200 and \leq 5000 mg/g). Treatment was continued if eGFR fell to levels below 25 mL/min/1.73 m².

The overall safety profile of dapagliflozin in patients with chronic kidney disease was consistent with the known safety profile of dapagliflozin.

Tabulated list of adverse reactions

The following adverse reactions have been identified in the placebo-controlled clinical studies and postmarketing surveillance. None were found to be dose-related. Adverse reactions listed below are classified according to frequency and system organ class (SOC). Frequency categories are defined according to the following convention: very common (\geq 1/10), common (\geq 1/100 to $<$ 1/10), uncommon (\geq 1/1,000 to $<$ 1/100), rare (\geq 1/10,000 to $<$ 1/1,000), very rare ($<$ 1/10,000), not known (cannot be estimated from the available data).

Table 2 Adverse reactions in placebo-controlled clinical studies^a and postmarketing experience

System organ class	Very common	Common*	Uncommon**	Rare	Very rare
<i>Infections and infestations</i>		Vulvovaginitis, balanitis and related genital infections ^{*b,c} Urinary tract infection ^{*b,d}	Fungal infection ^{**}		Necrotising fasciitis of the perineum (Fournier's gangrene) _{b,i}
<i>Metabolism and nutrition disorders</i>	Hypoglycaemia (when used with SU or insulin) ^b		Volume depletion ^{b,e} Thirst ^{**}	Diabetic ketoacidosis(when used in type 2 diabetes mellitus) _{b,i,k}	
<i>Nervous system disorders</i>		Dizziness			
<i>Gastrointestinal disorders</i>			Constipation ^{**} Dry mouth ^{**}		
<i>Skin and subcutaneous tissue disorders</i>		Rash ^j			angioedema
<i>Musculoskeletal and connective tissue disorders</i>		Back pain [*]			
<i>Renal and urinary disorders</i>		Dysuria Polyuria ^{*,f}	Nocturia ^{**}		

<i>Reproductive system and breast disorders</i>			Vulvovaginal pruritus** Pruritus genital**		
<i>Investigations</i>		Haematocrit increased ^g Creatinine renal clearance decreased during initial treatment ^b Dyslipidaemia ^h	Blood creatinine increased during initial treatment ^{**} , ^b Blood urea increased** Weight decreased**		

^aThe table shows up to 24-week (short-term) data regardless of glycaemic rescue.

^bSee corresponding subsection below for additional information.

^cVulvovaginitis, balanitis and related genital infections includes, e.g. the predefined preferred terms: vulvovaginal mycotic infection, vaginal infection, balanitis, genital infection fungal, vulvovaginal candidiasis, vulvovaginitis, balanitis candida, genital candidiasis, genital infection, genital infection male, penile infection, vulvitis, vaginitis bacterial, vulval abscess.

^dUrinary tract infection includes the following preferred terms, listed in order of frequency reported: urinary tract infection, cystitis, Escherichia urinary tract infection, genitourinary tract infection, pyelonephritis, trigonitis, urethritis, kidney infection and prostatitis.

^eVolume depletion includes, e.g. the predefined preferred terms: dehydration, hypovolaemia, hypotension.

^fPolyuria includes the preferred terms: pollakiuria, polyuria, urine output increased.

^gMean changes from baseline in haematocrit were 2.30 % for dapagliflozin 10 mg versus 0.33% for placebo. Haematocrit values >55% were reported in 1.3% of the subjects treated with dapagliflozin 10 mg versus 0.4% of placebo subjects.

^hMean percent change from baseline for dapagliflozin 10 mg versus placebo, respectively, was: total cholesterol 2.5% versus 0.0%; HDL cholesterol 6.0% versus 2.7%; LDL cholesterol 2.9% versus -1.0%; triglycerides -2.7% versus -0.7%.

ⁱSee section 4.4

^jAdverse reaction was identified through postmarketing surveillance. Rash includes the following preferred terms, listed in order of frequency in clinical studies : rash, rash generalised, rash pruritic, rash macular, rash maculo-papular, rash pustular, rash vesicular, and rash erythematous. In active- and placebo-controlled clinical studies (dapagliflozin, N=5936, All control, N=3403), the frequency of rash was similar for dapagliflozin (1.4%) and all control (1.4%), respectively.

^lReported in the cardiovascular outcomes study in patients with type 2 diabetes (DECLARE). Frequency is based on annual rate.

^{*}Reported in ≥ 2% of subjects and ≥ 1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

^{**}Reported by the investigator as possibly related, probably related or related to study treatment and reported in ≥ 0.2% of subjects and ≥ 0.1% more and at least 3 more subjects treated with dapagliflozin 10 mg compared to placebo.

Description of selected adverse reactions

Vulvovaginitis, balanitis and related genital infections

In the 13-study safety pool, vulvovaginitis, balanitis and related genital infections were reported in 5.5% and 0.6% of subjects who received dapagliflozin 10 mg and placebo, respectively. Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females (8.4% and 1.2% for dapagliflozin and placebo, respectively), and subjects with a prior history were more likely to have a recurrent infection.

In the DECLARE study, the numbers of patients with serious adverse events of genital infections were few and balanced: 2 patients in each of the dapagliflozin and placebo groups.

In the DAPA-HF study, no patient reported serious adverse events of genital infections in the dapagliflozin group and on in the placebo group. There were 7 (0.3%) patients with adverse events

leading to discontinuation due to genital infections in the dapagliflozin group and none in the placebo group

In the DAPA-CKD study, there were 3 (0.1%) patients with serious adverse events of genital infections in the dapagliflozin group and none in the placebo group. There were 3 (0.1%) patients with adverse events leading to discontinuation due to genital infections in the dapagliflozin group and none in the placebo group. Serious adverse events of genital infections or adverse events leading to discontinuation due to genital infections were not reported for any patients without diabetes.

Necrotising fasciitis of the perineum (Fournier's gangrene)

Cases of Fournier's gangrene have been reported postmarketing in patients taking SGLT2 inhibitors, including dapagliflozin (see section 4.4).

In the DECLARE study with 17,160 type 2 diabetes mellitus patients and a median exposure time of 48 months, a total of 6 cases of Fournier's gangrene were reported, one in the dapagliflozin-treated group and 5 in the placebo group.

Hypoglycaemia

The frequency of hypoglycaemia depended on the type of background therapy used in the clinical studies in diabetes mellitus.

For studies of dapagliflozin in monotherapy, as add-on to metformin or as add-on to sitagliptin (with or without metformin), the frequency of minor episodes of hypoglycaemia was similar (< 5%) between treatment groups, including placebo up to 102 weeks of treatment. Across all studies, major events of hypoglycaemia were uncommon and comparable between the groups treated with dapagliflozin or placebo. Studies with add-on sulphonylurea and add-on insulin therapies had higher rates of hypoglycaemia (see section 4.5).

In an add-on to glimepiride study, at Weeks 24 and 48, minor episodes of hypoglycaemia were reported more frequently in the group treated with dapagliflozin 10 mg plus glimepiride (6.0% and 7.9%, respectively) than in the placebo plus glimepiride group (2.1% and 2.1%, respectively).

In an add-on to insulin study, episodes of major hypoglycaemia were reported in 0.5% and 1.0% of subjects treated with dapagliflozin 10 mg plus insulin at Weeks 24 and 104, respectively, and in 0.5% of subjects treated with placebo plus insulin groups at Weeks 24 and 104. At Weeks 24 and 104, minor episodes of hypoglycaemia were reported, respectively, in 40.3% and 53.1% of subjects who received dapagliflozin 10 mg plus insulin and in 34.0% and 41.6% of the subjects who received placebo plus insulin.

In an add-on to metformin and a sulphonylurea study, up to 24 weeks, no episodes of major hypoglycaemia were reported. Minor episodes of hypoglycaemia were reported in 12.8% of subjects who received dapagliflozin 10 mg plus metformin and a sulphonylurea and in 3.7% of subjects who received placebo plus metformin and a sulphonylurea.

In the DECLARE study, no increased risk of major hypoglycaemia was observed with dapagliflozin therapy compared with placebo. Major events of hypoglycaemia were reported in 58 (0.7%) patients treated with dapagliflozin and 83 (1.0%) patients treated with placebo.

In the DAPA-HF study, major events of hypoglycaemia were reported in 4 (0.2%) patients in both the dapagliflozin and placebo treatment groups and observed only in patients with 2 diabetes mellitus

In the DAPA-CKD study, major events of hypoglycaemia were reported in 14 (0.7%) patients in the dapagliflozin group and 28 (1.3%) patients in the placebo group and observed only in patients with type 2 diabetes mellitus

Volume depletion

In the 13-study safety pool reactions suggestive of volume depletion (including, reports of dehydration, hypovolaemia or hypotension) were reported in 1.1% and 0.7% of subjects who received dapagliflozin 10 mg and placebo, respectively; serious reactions occurred in < 0.2% of subjects balanced between dapagliflozin 10 mg and placebo (see section 4.4).

In the DECLARE study, the numbers of patients with events suggestive of volume depletion were balanced between treatment groups: 213 (2.5%) and 207 (2.4%) in the dapagliflozin and placebo groups, respectively. Serious adverse events were reported in 81 (0.9%) and 70 (0.8%) in the dapagliflozin and placebo group, respectively. Events were generally balanced between treatment groups across subgroups of age, diuretic use, blood pressure and angiotensin converting enzyme inhibitors (ACE-I/angiotensin II type 1 receptor blockers (ARB) use. In patients with eGFR < 60 mL/min/1.73 m² at baseline, there were 19 events of serious adverse events suggestive of volume depletion in the dapagliflozin group and 13 events in the placebo group.

In the DAPA-HF study, the numbers of patients with events suggestive of volume depletion were 170 (7.2%) in the dapagliflozin group and 153 (6.5%) in the placebo group. There were fewer patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group (23 [1.0%]) compared with the placebo group (38 [1.6%]). Results were similar irrespective of presence of diabetes at baseline and baseline eGFR

In the DAPA-CKD study, the numbers of patients with events suggestive of volume depletion were 120 (5.6%) in the dapagliflozin group and 84 (3.9%) in the placebo group. There were 16 (0.7%) patients with serious events of symptoms suggestive of volume depletion in the dapagliflozin group and 15 (0.7%) patients in the placebo group.

Diabetic ketoacidosis in type 2 diabetes mellitus

In the DECLARE study, with a median exposure time of 48 months, events of DKA were reported in 27 patients in the dapagliflozin 10 mg group and 12 patients in the placebo group. The events occurred evenly distributed over the study period. Of the 27 patients with DKA events in the dapagliflozin group, 22 had concomitant insulin treatment at the time of the event. Precipitating factors for DKA were as expected in a type 2 diabetes mellitus population (see section 4.4).

In the DAPA-HF study, events of DKA were reported in 3 patients with type 2 diabetes mellitus in the dapagliflozin group and none in the placebo group

In the DAPA-CKD study, events of DKA were not reported in any patient in the dapagliflozin group and in 2 patients with type 2 diabetes mellitus in the placebo group.

Urinary tract infections

In the 13-study safety pool, urinary tract infections were more frequently reported for dapagliflozin 10 mg compared to placebo (4.7% versus 3.5%, respectively; see section 4.4). Most infections were mild to moderate, and subjects responded to an initial course of standard treatment and rarely resulted in discontinuation from dapagliflozin treatment. These infections were more frequent in females, and subjects with a prior history were more likely to have a recurrent infection.

In the DECLARE study, serious events of urinary tract infections were reported less frequently for dapagliflozin 10 mg compared with placebo, 79 (0.9%) events versus 109 (1.3%) events, respectively.

In the DAPA-HF study, the numbers of patients with serious adverse events of urinary tract infections were 14 (0.6%) in the dapagliflozin group and 17 (0.7%) in the placebo group. There were 5 (0.2%) patients with adverse events leading to discontinuation due to urinary tract infections in each of the dapagliflozin and placebo groups

In the DAPA-CKD study, the numbers of patients with serious adverse events of urinary tract infections were 29 (1.3%) in the dapagliflozin group and 18 (0.8%) in the placebo group. There were 8 (0.4%) patients with adverse events leading to discontinuations due to urinary tract

infections in the dapagliflozin group and 3 (0.1%) in the placebo group. The numbers of patients without diabetes reporting serious adverse events of urinary tract infections or adverse events leading to discontinuation due to urinary tract infections were similar between treatment groups (6 [0.9%] versus 4 [0.6%] for serious adverse events, and 1 [0.1%] versus 0 for adverse events leading to discontinuation, in the dapagliflozin and placebo groups, respectively).

Increased creatinine

Adverse reactions related to increased creatinine were grouped (e.g. decreased renal creatinine clearance, renal impairment, increased blood creatinine and decreased glomerular filtration rate). In the 13-study safety pool this grouping of reactions was reported in 3.2% and 1.8% of patients who received dapagliflozin 10 mg and placebo, respectively. In patients with normal renal function or mild renal impairment (baseline eGFR \geq 60 mL/min/1.73m²) this grouping of reactions were reported in 1.3% and 0.8% of patients who received dapagliflozin 10 mg and placebo, respectively. These reactions were more common in patients with baseline eGFR \geq 30 and $<$ 60 mL/min/1.73m² (18.5% dapagliflozin 10 mg vs 9.3% placebo).

Further evaluation of patients who had renal-related adverse events showed that most had serum creatinine changes of \leq 0.5 mg/dL from baseline. The increases in creatinine were generally transient during continuous treatment or reversible after discontinuation of treatment.

In the DECLARE study, including elderly patients and patients with renal impairment (eGFR less than 60 mL/min/1.73 m²), eGFR decreased over time in both treatment groups. At 1 year, mean eGFR was slightly lower, and at 4 years, mean eGFR was slightly higher in the dapagliflozin group compared with the placebo group.

In the DAPA-HF study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial decrease in mean eGFR was -4.3 mL/min/1.73 m² in the dapagliflozin group and -1.1 mL/min/1.73 m² in the placebo group. At 20 months, change from baseline in eGFR was similar between the treatment groups: -5.3 mL/min/1.73 m² for dapagliflozin and -4.5 mL/min/1.73 m² for placebo.

In the DAPA-CKD study, eGFR decreased over time in both the dapagliflozin group and the placebo group. The initial (day 14) decrease in mean eGFR was -4.0 mL/min/1.73 m² in the dapagliflozin group and -0.8 mL/min/1.73 m² in the placebo group. At 28 months, change from baseline in eGFR was -7.4 mL/min/1.73 m² in the dapagliflozin group and -8.6 mL/min/1.73 m² in the placebo group.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

<https://sideeffects.health.gov.il>

4.9 Overdose

Dapagliflozin did not show any toxicity in healthy subjects at single oral doses up to 500 mg (50 times the maximum recommended human dose). These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500 mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100 mg (10 times the maximum recommended human dose) were administered for 2 weeks in healthy subjects and type 2 diabetes subjects, the incidence of hypoglycaemia was slightly higher than placebo and was not dose-related. Rates of adverse events including dehydration or hypotension were similar to placebo, and there were no clinically

meaningful dose-related changes in laboratory parameters, including serum electrolytes and biomarkers of renal function.

In the event of an overdose, appropriate supportive treatment should be initiated as dictated by the patient's clinical status. The removal of dapagliflozin by haemodialysis has not been studied.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs used in diabetes, Sodium glucose co-transporter (SGLT-2)
ATC code: A10BK01

Mechanism of action

Dapagliflozin is a highly potent (K_i : 0.55 nM), selective and reversible inhibitor of SGLT2.

Inhibition of SGLT2 by dapagliflozin reduces reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which increases tubuloglomerular feedback and reduces intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and preserve renal function. Other effects include an increase in haematocrit and reduction in body weight. The cardiac and renal benefits of dapagliflozin are not solely dependent on the blood glucoselowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF and DAPACKD studies

Dapagliflozin improves both fasting and post-prandial plasma glucose levels by reducing renal glucose reabsorption leading to urinary glucose excretion. This glucose excretion (glucuretic effect) is observed after the first dose, is continuous over the 24-hour dosing interval and is sustained for the duration of treatment. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and GFR. Thus, in subjects with normal blood glucose, dapagliflozin has a low propensity to cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. Dapagliflozin acts independently of insulin secretion and insulin action. Improvement in homeostasis model assessment for beta cell function (HOMA beta-cell) has been observed in clinical studies with dapagliflozin.

The SGLT2 is selectively expressed in the kidney. Dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is > 1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

Pharmacodynamic effects

Increases in the amount of glucose excreted in the urine were observed in healthy subjects and in subjects with type 2 diabetes mellitus following the administration of dapagliflozin. Approximately 70 g of glucose was excreted in the urine per day (corresponding to 280 kcal/day) at a dapagliflozin dose of 10 mg/day in subjects with type 2 diabetes mellitus for 12 weeks. Evidence of sustained glucose excretion was seen in subjects with type 2 diabetes mellitus given dapagliflozin 10 mg/day for up to 2 years.

This urinary glucose excretion with dapagliflozin also results in osmotic diuresis and increases in urinary volume in subjects with type 2 diabetes mellitus. Urinary volume increases in subjects with type 2 diabetes mellitus treated with dapagliflozin 10 mg were sustained at 12 weeks and

amounted to approximately 375 ml/day. The increase in urinary volume was associated with a small and transient increase in urinary sodium excretion that was not associated with changes in serum sodium concentrations.

Urinary uric acid excretion was also increased transiently (for 3-7 days) and accompanied by a sustained reduction in serum uric acid concentration. At 24 weeks, reductions in serum uric acid concentrations ranged from -48.3 to -18.3 micromoles/l (-0.87 to -0.33 mg/dl).

Clinical efficacy and safety

Type 2 diabetes mellitus

improvement of glycaemic control and reduction of cardiovascular and renal morbidity and mortality are integral parts of the treatment of type 2 diabetes.

Fourteen double-blind, randomised, controlled clinical studies were conducted with 7,056 subjects with type 2 diabetes to evaluate the glycaemic efficacy and safety of Forxiga; 4,737 subjects in these studies were treated with dapagliflozin. Twelve studies had a treatment period of 24 weeks duration, 8 with long-term extensions ranging from 24 to 80 weeks (up to a total study duration of 104 weeks), one study had a 28-week treatment period. and one study was 52 weeks in duration with long-term extensions of 52 and 104 weeks (total study duration of 208 weeks). Mean duration of diabetes ranged from 1.4 to 16.9 years. Fifty percent (50%) had mild renal impairment and 11% had moderate renal impairment. Fifty-one percent (51%) of the subjects were men, 84% were White, 8% were Asian, 4% were Black and 4% were of other racial groups. Eighty-one percent (81%) of the subjects had a body mass index (BMI) \geq 27. Furthermore, two 12-week, placebo-controlled studies were conducted in patients with inadequately controlled type 2 diabetes and hypertension.

A cardiovascular outcome study (DECLARE) was conducted with dapagliflozin 10 mg compared with placebo in 17,160 patients with type 2 diabetes mellitus with or without established cardiovascular disease to evaluate the effect on cardiovascular and renal events.

Glycaemic control

Monotherapy

A double-blind, placebo-controlled study of 24-week duration (with an additional extension period) was conducted to evaluate the safety and efficacy of monotherapy with Forxiga in subjects with inadequately controlled type 2 diabetes mellitus. Once-daily treatment with dapagliflozin resulted in statistically significant ($p < 0.0001$) reductions in HbA1c compared to placebo (Table 2).

In the extension period, HbA1c reductions were sustained through Week 102 (-0.61%, and -0.17% adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively).

Table 3 Results at Week 24 (LOCF^a) of a placebo-controlled study of dapagliflozin as monotherapy

	Monotherapy	
	Dapagliflozin 10 mg	Placebo
N^b	70	75
HbA1c (%)	8.01	7.79
Baseline (mean)	-0.89	-0.23
Change from baseline ^c	-0.66*	
Difference from placebo ^c (95% CI)	(-0.96, -0.36)	
Subjects (%) achieving: HbA1c < 7%	50.8 ^s	31.6
Adjusted for baseline		
Body weight (kg)	94.13	88.77
Baseline (mean)	-3.16	-2.19

Change from baseline ^c Difference from placebo ^c (95% CI)	-0.97 (-2.20, 0.25)	
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^aLOCF: Last observation (prior to rescue for rescued subjects) carried forward

^bAll randomised subjects who took at least one dose of double-blind study medication during the short-term double-blind period

^cLeast squares mean adjusted for baseline value

^{*}p-value < 0.0001 versus placebo

[§] Not evaluated for statistical significance as a result of the sequential testing procedure for secondary end points

Add-on Combination therapy

In a 52-week, active-controlled non-inferiority study (with 52- and 104-week extension periods), Forxiga was evaluated as add-on therapy to metformin compared with a sulphonylurea (glipizide) as add-on therapy to metformin in subjects with inadequate glycaemic control (HbA1c > 6.5% and ≤ 10%). The results showed a similar mean reduction in HbA1c from baseline to Week 52, compared to glipizide, thus demonstrating non-inferiority (Table 4). At Week 104, adjusted mean change from baseline in HbA1c was -0.32% for dapagliflozin and -0.14% for glipizide. At Week 208, adjusted mean change from baseline in HbA1c was -0.10% for dapagliflozin and 0.20% for glipizide. At 52, 104 and 208 weeks, a significantly lower proportion of subjects in the group treated with dapagliflozin (3.5%, 4.3% and 5.0%, respectively) experienced at least one event of hypoglycaemia compared to the group treated with glipizide (40.8%, 47.0% and 50.0%, respectively). The proportion of subjects remaining in the study at Week 104 and Week 208 was 56.2% and 39.7% for the group treated with dapagliflozin and 50.0% and 34.6% for the group treated with glipizide.

Table 4. Results at Week 52 (LOCF^a) in an active-controlled study comparing dapagliflozin to glipizide as add-on to metformin

Parameter	Dapagliflozin + metformin	Glipizide + metformin
N^b	400	401
HbA1c (%)	7.69	7.74
Baseline (mean)	-0.52	-0.52
Change from baseline ^c	0.00 ^d	
Difference from glipizide + metformin ^c (95% CI)	(-0.11, 0.11)	
Body weight (kg)	88.44	87.60
Baseline (mean)	-3.22	1.44
Change from baseline ^c	-4.65 [*]	
Difference from glipizide + metformin ^c (95% CI)	(-5.14, -4.17)	

^aLOCF: Last observation carried forward

^bRandomised and treated subjects with baseline and at least 1 post-baseline efficacy measurement

^cLeast squares mean adjusted for baseline value

^dNon-inferior to glipizide + metformin

^{*}p-value < 0.0001

Dapagliflozin as an add-on with either metformin, glimepiride, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in HbA1c at 24 weeks compared with subjects receiving placebo (p < 0.0001; Tables 5, 6 and 7).

The reductions in HbA1c observed at Week 24 were sustained in add-on combination studies (glimepiride and insulin) with 48-week data (glimepiride) and up to 104-week data (insulin). At Week 48 when added to sitagliptin (with or without metformin), the adjusted mean change from baseline for dapagliflozin 10 mg and placebo was -0.30% and 0.38%, respectively. For the add-on

to metformin study, HbA1c reductions were sustained through Week 102 (-0.78% and 0.02% adjusted mean change from baseline for 10 mg and placebo, respectively). At Week 104 for insulin (with or without additional oral glucose-lowering medicinal products), the HbA1c reductions were -0.71% and -0.06% adjusted mean change from baseline for dapagliflozin 10 mg and placebo, respectively. At Weeks 48 and 104, the insulin dose remained stable compared to baseline in subjects treated with dapagliflozin 10 mg at an average dose of 76 IU/day. In the placebo group there was a mean increase of 10.5 IU/day and 18.3 IU/day from baseline (mean average dose of 84 and 92 IU/day) at Weeks 48 and 104, respectively. The proportion of subjects remaining in the study at Week 104 was 72.4% for the group treated with dapagliflozin 10 mg and 54.8% for the placebo group.

Table 5 Results of 24-week (LOCF^a) placebo-controlled studies of dapagliflozin in add-on combination with metformin or sitagliptin (with or without metformin)

	Add-on combination			
	Metformin ¹		DPP-4 Inhibitor (sitagliptin ²) ± Metformin ¹	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
N^b	135	137	223	224
HbA1c (%)	7.92	8.11	7.90	7.97
Baseline (mean)	-0.84	-0.30	-0.45	0.04
Change from baseline ^c	-0.54*		-0.48*	
Difference from placebo ^c (95% CI)	(-0.74, -0.34)		(-0.62, -0.34)	
Subjects (%) achieving: HbA1c < 7% Adjusted for baseline	40.6**	25.9		
Body weight (kg)	86.28	87.74	91.02	89.23
Baseline (mean)	-2.86	-0.89	-2.14	-0.26
Change from baseline ^c	-1.97*		-1.89*	
Difference from placebo ^c (95% CI)	(-2.63, -1.31)		(-2.37, -1.40)	

¹Metformin ≥ 1500 mg/day; ²sitagliptin 100 mg/day

^aLOCF: Last observation (prior to rescue for rescued subjects) carried forward

^bAll randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double-blind period

^cLeast squares mean adjusted for baseline value

*p-value < 0.0001 versus placebo + oral glucose-lowering medicinal product

**p-value < 0.05 versus placebo + oral glucose-lowering medicinal product

Table 6. Results of 24-week placebo-controlled studies of dapagliflozin in add-on combination with sulphonylurea (glimepiride) or metformin and a sulphonylurea

	Add-on combination			
	Sulphonylurea (glimepiride ¹)		Sulphonylurea + Metformin ²	
	Dapagliflozin 10 mg	Placebo	Dapagliflozin 10 mg	Placebo
N^a	151	145	108	108
HbA1c (%)^b	8.07	8.15	8.08	8.24
Baseline (mean)	-0.82	-0.13	-0.86	-0.17
Change from Baseline ^c	-0.68*		-0.69*	
Difference from Placebo ^c (95% CI)	(-0.86, -0.51)		(-0.89, -0.49)	
Subjects (%) achieving: HbA1c < 7% (LOCF)^d	31.7*	13.0	31.8*	11.1

Adjusted for baseline				
Body weight (kg) (LOCF)^d	80.56	80.94	88.57	90.07
Baseline (mean)	-2.26	-0.72	-2.65	-0.58
Change from Baseline ^c	-1.54*		-2.07*	
Difference from Placebo ^c (95% CI)	(-2.17, -0.92)		(-2.79, -1.35)	

¹glimepiride 4 mg/day; ²Metformin (immediate- or extended-release formulations) ≥ 1500 mg/day plus maximum tolerated dose, which must be at least half maximum dose, of a sulphonylurea for at least 8 weeks prior to enrollment.

^aRandomized and treated patients with baseline and at least 1 post-baseline efficacy measurement.

^bColumns 1 and 2, HbA1c analyzed using LOCF (see footnote d); Columns 3 and 4, HbA1c analyzed using LRM (see footnote e)

^cLeast squares mean adjusted for baseline value

^dLOCF: Last observation (prior to rescue for rescued subjects) carried forward

^eLRM: Longitudinal repeated measures analysis

*p-value < 0.0001 versus placebo + oral glucose-lowering medicinal product(s)

Table 7. Results at Week 24 (LOCF^a) in a placebo-controlled study of dapagliflozin in combination with insulin (alone or with oral glucose-lowering medicinal products)

Parameter	Dapagliflozin 10 mg + insulin \pm oral glucose-lowering medicinal products ²	Placebo + insulin \pm oral glucose-lowering medicinal products ²
N^b	194	193
HbA1c (%)	8.58	8.46
Baseline (mean)	-0.90	-0.30
Change from baseline ^c	-0.60*	
Difference from placebo ^c (95% CI)	(-0.74, -0.45)	
Body weight (kg)	94.63	94.21
Baseline (mean)	-1.67	0.02
Change from baseline ^c	-1.68*	
Difference from placebo ^c (95% CI)	(-2.19, -1.18)	
Mean daily insulin dose (IU)¹	77.96	73.96
Baseline (mean)	-1.16	5.08
Change from baseline ^c	-6.23*	11.0
Difference from placebo ^c (95% CI)	(-8.84, -3.63)	
Subjects with mean daily insulin dose reduction of at least 10% (%)	19.7**	

^aLOCF: Last observation (prior to or on the date of the first insulin up-titration, if needed) carried forward

^bAll randomised subjects who took at least one dose of double-blind study medicinal product during the short-term double-blind period

^cLeast squares mean adjusted for baseline value and presence of oral glucose-lowering medicinal product

*p-value < 0.0001 versus placebo + insulin \pm oral glucose-lowering medicinal product

**p-value < 0.05 versus placebo + insulin \pm oral glucose-lowering medicinal product

¹Up-titration of insulin regimens (including short-acting, intermediate, and basal insulin) was only allowed if subjects met pre-defined FPG criteria.

²Fifty percent of subjects were on insulin monotherapy at baseline; 50% were on 1 or 2 oral glucose-lowering medicinal product(s) in addition to insulin: Of this latter group, 80% were on metformin alone, 12% were on metformin plus sulphonylurea therapy, and the rest were on other oral glucose-lowering medicinal products.

In combination with metformin in drug-naive patients

A total of 1,236 drug-naive patients with inadequately controlled type 2 diabetes (HbA1c $\geq 7.5\%$ and $\leq 12\%$) participated in two active-controlled studies of 24 weeks duration to evaluate the

efficacy and safety of dapagliflozin (5 mg or 10 mg) in combination with metformin in drug-naive patients versus therapy with the monocomponents.

Treatment with dapagliflozin 10 mg in combination with metformin (up to 2000 mg per day) provided significant improvements in HbA1c compared to the individual components (Table 7), and led to greater reductions in fasting plasma glucose (FPG) (compared to the individual components) and body weight (compared to metformin).

Table 8: Results at Week 24 (LOCFa) in an active-controlled study of dapagliflozin and metformin combination therapy in drug-naive patients

Parameter	Dapagliflozin 10 mg + Metformin	Dapagliflozin 10 mg	Metformin
N ^b	211 ^b	219 ^b	208 ^b
HbA1c (%)			
Baseline (mean)	9.10	9.03	9.03
Change from baseline ^c	-1.98	-1.45	-1.44
Difference from dapagliflozin ^c	-0.53*		
(95% CI)	(-0.74, -0.32)		
Difference from metformin ^c	-0.54*	-0.01	
(95% CI)	(-0.75, -0.33)	(-0.22, 0.20)	

^aLOCF: last observation (prior to rescue for rescued patients) carried forward.

^bAll randomised patients who took at least one dose of double-blind study medication during the short-term double-blind period.

^cLeast squares mean adjusted for baseline value.

*p-value <0.0001.

Combination therapy with prolonged-release exenatide

In a 28-week, double-blind, active comparator-controlled study, the combination of dapagliflozin and prolonged-release exenatide (a GLP-1 receptor agonist) was compared to dapagliflozin alone and prolonged-release exenatide alone in subjects with inadequate glycaemic control on metformin alone (HbA1c ≥ 8% and ≤ 12%). All treatment groups had a reduction in HbA1c compared to baseline. The combination treatment with dapagliflozin 10 mg and prolonged-release exenatide group showed superior reductions in HbA1c from baseline compared to dapagliflozin alone and prolonged-release exenatide alone (Table 9).

Table 9. Results of one 28-week study of dapagliflozin and prolonged-release exenatide versus dapagliflozin alone and prolonged-release exenatide alone, in combination with metformin (intent to treat patients)

Parameter	Dapagliflozin 10 mg QD + Prolonged-release exenatide 2 mg QW	Dapagliflozin 10 mg QD+ Placebo QW	Prolonged-release exenatide 2 mg QW+ Placebo QD
N	228	230	227
HbA1c (%)			
Baseline (mean)	9.29	9.25	9.26
Change from baseline ^a	-1.98	-1.39	-1.60
Mean difference in change from baseline between combination		-0.59* (-0.84, -0.34)	-0.38** (-0.63, -0.13)

and single active agent (95% CI)			
Subjects (%) achieving HbA1c < 7%	44.7	19.1	26.9
Body weight (kg)			
Baseline (mean)	92.13	90.87	89.12
Change from baseline ^a	-3.55	-2.22	-1.56
Mean difference in change from baseline between combination and single active agent (95% CI)		-1.33* (-2.12, -0.55)	-2.00* (-2.79, -1.20)

QD=once daily, QW=once weekly, N=number of patients, CI=confidence interval.

aAdjusted least squares means (LS Means) and treatment group difference(s) in the change from baseline values

at Week 28 are modelled using a mixed model with repeated measures (MMRM) including treatment, region, baseline HbA1c stratum (< 9.0% or ≥ 9.0%), week, and treatment by week interaction as fixed factors, and baseline value as a covariate.

*p < 0.001, **p < 0.01.

P-values are all adjusted p-values for multiplicity.

Analyses exclude measurements post rescue therapy and post premature discontinuation of study medicinal product.

Fasting plasma glucose

Treatment with dapagliflozin 10 mg as a monotherapy or as an add-on to either metformin, glimepiride, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant reductions in FPG (-1.90 to -1.20 mmol/l [-34.2 to -21.7 mg/dl]) compared to placebo (-0.33 to 0.21 mmol/l [-6.0 to 3.8 mg/dl]). This effect was observed at Week 1 of treatment and maintained in studies extended through Week 104.

Combination therapy of dapagliflozin 10 mg and prolonged-release exenatide resulted in significantly greater reductions in FPG at Week 28: -3.66 mmol/l (-65.8 mg/dl), compared to -2.73 mmol/l (-49.2 mg/dl) for dapagliflozin alone (p < 0.001) and -2.54 mmol/l (-45.8 mg/dl) for exenatide alone (p < 0.001).

In a dedicated study in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m², treatment with dapagliflozin demonstrated reductions in FPG at Week 24: -1.19 mmol/L (-21.46 mg/dL) compared to -0.27 mmol/L (-4.87 mg/dL) for placebo (p=0.001).

Post-prandial glucose

Treatment with dapagliflozin 10 mg as an add-on to glimepiride resulted in statistically significant reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to Week 48.

Treatment with dapagliflozin 10 mg as an add-on to sitagliptin (with or without metformin) resulted in reductions in 2-hour post-prandial glucose at 24 weeks that were maintained up to Week 48.

Combination therapy of dapagliflozin 10 mg and prolonged-release exenatide resulted in significantly greater reductions in 2-hour post-prandial glucose at Week 28 compared to either agent alone.

Body weight

Dapagliflozin 10 mg as an add-on to metformin, glimepiride, metformin and a sulphonylurea, sitagliptin (with or without metformin) or insulin resulted in statistically significant body weight reduction at 24 weeks (p < 0.0001, Tables 5 and 6). These effects were sustained in longer-term studies. At 48 weeks, the difference for dapagliflozin as add-on to sitagliptin (with or without metformin) compared with placebo was -2.22 kg. At 102 weeks, the difference for dapagliflozin as

add-on to metformin compared with placebo, or as add-on to insulin compared with placebo was -2.14 and -2.88 kg, respectively.

As an add-on therapy to metformin in an active-controlled non-inferiority study, dapagliflozin resulted in a statistically significant body weight reduction compared with glipizide of -4.65 kg at 52 weeks ($p < 0.0001$, Table 3) that was sustained at 104 and 208 weeks (-5.06 kg and -4.38 kg, respectively).

The combination of dapagliflozin 10 mg and prolonged-release exenatide demonstrated significantly greater weight reductions compared to either medicinal product alone (Table 9).

A 24-week study in 182 diabetic subjects using dual energy X-ray absorptiometry (DXA) to evaluate body composition demonstrated reductions with dapagliflozin 10 mg plus metformin compared with placebo plus metformin, respectively, in body weight and body fat mass as measured by DXA rather than lean tissue or fluid loss. Treatment with Forxiga plus metformin showed a numerical decrease in visceral adipose tissue compared with placebo plus metformin treatment in a magnetic resonance imaging substudy.

Blood pressure

In a pre-specified pooled analysis of 13 placebo-controlled studies, treatment with dapagliflozin 10 mg resulted in a systolic blood pressure change from baseline of -3.7 mmHg and diastolic blood pressure of -1.8 mmHg versus -0.5 mmHg systolic and -0.5 mmHg diastolic blood pressure for placebo group at Week 24. Similar reductions were observed up to 104 weeks.

Combination therapy of dapagliflozin 10 mg and prolonged-release exenatide resulted in a significantly greater reduction in systolic blood pressure at Week 28 (-4.3 mmHg) compared to dapagliflozin alone (-1.8 mmHg, $p < 0.05$) and prolonged-release exenatide alone (-1.2 mmHg, $p < 0.01$).

In two 12-week, placebo-controlled studies a total of 1,062 patients with inadequately controlled type 2 diabetes and hypertension (despite pre-existing stable treatment with an ACE-I or ARB in one study and an ACE-I or ARB plus one additional antihypertensive treatment in another study) were treated with dapagliflozin 10 mg or placebo. At Week 12 for both studies, dapagliflozin 10 mg plus usual antidiabetic treatment provided improvement in HbA1c and decreased the placebo-corrected systolic blood pressure on average by 3.1 and 4.3 mmHg, respectively.

In a dedicated study in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m², treatment with dapagliflozin demonstrated reductions in seated systolic blood pressure at Week 24: -4.8 mmHg compared to -1.7 mmHg for placebo ($p < 0.05$).

Glycaemic control in patients with Moderate renal impairment CKD 3A (eGFR ≥ 45 to < 60 ml/min/1.73 m²)

The efficacy of dapagliflozin was assessed in a dedicated study in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m² who had inadequate glycaemic control on usual care. Treatment with dapagliflozin resulted in reductions in HbA1c and body weight compared with placebo (Table 10).

Table 10. Results at Week 24 of a placebo-controlled study of dapagliflozin in diabetic patients with an eGFR ≥ 45 to < 60 mL/min/1.73 m²

	Dapagliflozin ^a 10 mg	Placebo ^a
N ^b	159	161
HbA1c (%)		
Baseline (mean)	8.35	8.03
Change from baseline ^b	-0.37	-0.03
Difference from placebo ^b (95% CI)	-0.34* (-0.53, -0.15)	
Body weight (kg)		
Baseline (mean)	92.51	88.30
Percent change from baseline ^c	-3.42	-2.02
Difference in percent change from placebo ^c (95% CI)	-1.43* (-2.15, -0.69)	

^a Metformin or metformin hydrochloride were part of the usual care in 69.4% and 64.0% of the patients for the dapagliflozin and placebo groups, respectively.
^b Least squares mean adjusted for baseline value
^c Derived from least squares mean adjusted for baseline value
* p<0.001

Patients with baseline HbA1c ≥ 9%

In a pre-specified analysis of subjects with baseline HbA1c ≥ 9.0%, treatment with dapagliflozin 10 mg resulted in statistically significant reductions in HbA1c at Week 24 as a monotherapy (adjusted mean change from baseline: - 2.04% and 0.19% for dapagliflozin 10 mg and placebo, respectively) and as an add-on to metformin (adjusted mean change from baseline: -1.32% and -0.53% for dapagliflozin and placebo, respectively).

Cardiovascular and renal outcomes

Dapagliflozin Effect on Cardiovascular Events (DECLARE) was an international, multicentre, randomised, double-blind, placebo-controlled clinical study conducted to determine the effect of dapagliflozin compared with placebo on cardiovascular outcomes when added to current background therapy. All patients had type 2 diabetes mellitus and either at least two additional cardiovascular risk factors (age ≥ 55 years in men or ≥ 60 years in women and one or more of dyslipidaemia, hypertension or current tobacco use) or established cardiovascular disease.

Of 17,160 randomised patients, 6,974 (40.6%) had established cardiovascular disease and 10,186 (59.4%) did not have established cardiovascular disease. 8,582 patients were randomised to dapagliflozin 10 mg and 8,578 to placebo and were followed for a median of 4.2 years.

The mean age of the study population was 63.9 years, 37.4% were female. In total, 22.4% had had diabetes for ≤ 5 years, mean duration of diabetes was 11.9 years. Mean HbA1c was 8.3% and mean BMI was 32.1 kg/m².

At baseline, 10.0% of patients had a history of heart failure. Mean eGFR was 85.2 mL/min/1.73 m², 7.4% of patients had eGFR < 60 mL/min/1.73 m², and 30.3% of patients had micro- or macroalbuminuria ([UACR] ≥ 30 to ≤ 300 mg/g or > 300 mg/g, respectively).

Most patients (98%) used one or more diabetic medicinal products at baseline, including metformin (82%), insulin (41%) and sulfonylurea (43%),

The primary endpoints were time to first event of the composite of cardiovascular death, myocardial infarction or ischaemic stroke (MACE) and time to first event of the composite of hospitalisation for heart failure or cardiovascular death. The secondary endpoints were a renal composite endpoint and all-cause mortality.

Major adverse cardiovascular events

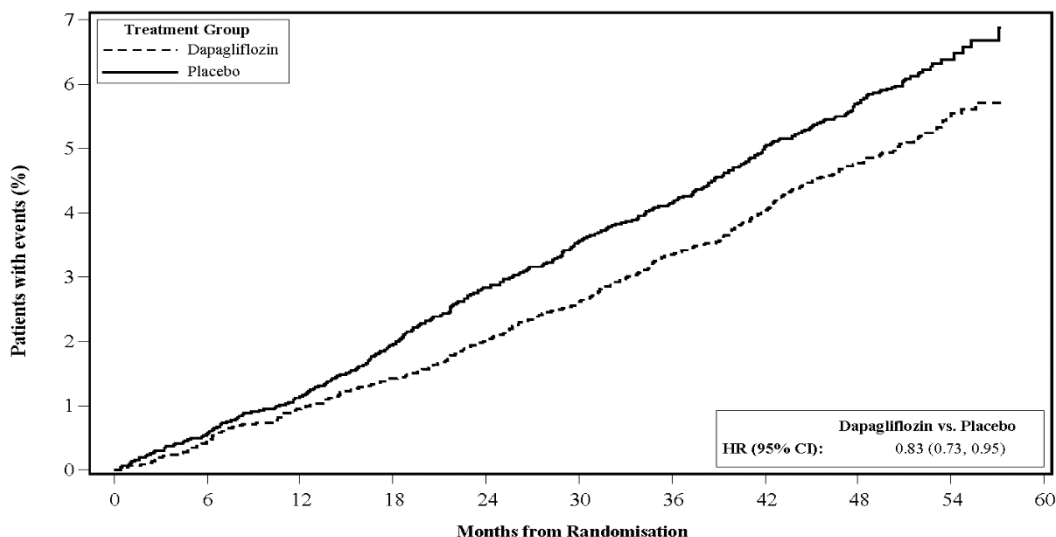
Dapagliflozin 10 mg demonstrated non-inferiority versus placebo for the composite of cardiovascular death, myocardial infarction or ischaemic stroke (one-sided p < 0.001).

Heart failure or cardiovascular death

Dapagliflozin 10 mg demonstrated superiority versus placebo in preventing the composite of hospitalisation for heart failure or cardiovascular death (Figure 1). The difference in treatment effect was driven by hospitalisation for heart failure, with no difference in cardiovascular death (Figure 2).

The treatment benefit of dapagliflozin over placebo was observed both in patients with and without established cardiovascular disease, with and without heart failure at baseline, and was consistent across key subgroups, including age, gender, renal function (eGFR) and region.

Figure 1: Time to first occurrence of hospitalisation for heart failure or cardiovascular death



Patients at risk

Dapagliflozin:	8582	8517	8415	8322	8224	8110	7970	7497	5445	1626
Placebo:	8578	8485	8387	8259	8127	8003	7880	7367	5362	1573

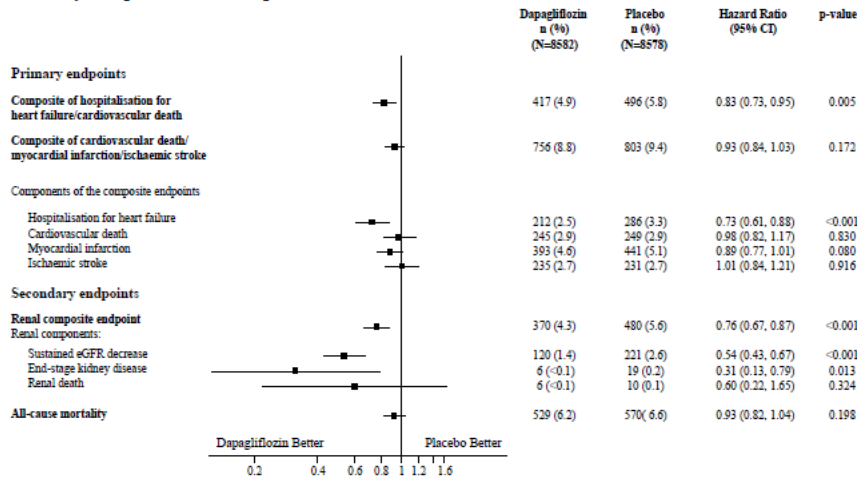
Patients at risk is the number of patients at risk at the beginning of the period.

HR=Hazard ratio CI=Confidence interval.

Results on primary and secondary endpoints are displayed in Figure 2. Superiority of dapagliflozin over placebo was not demonstrated for MACE ($p=0.172$). The renal composite endpoint and all-cause mortality were therefore not tested as part of the confirmatory testing procedure.

Figure 2: Treatment effects for the primary composite endpoints and their components, and the secondary endpoints and components

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Renal composite endpoint defined as: sustained confirmed $\geq 40\%$ decrease in eGFR to eGFR <60 mL/min/1.73 m² and/or end-stage kidney disease (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 mL/min/1.73 m²) and/or renal or cardiovascular death.

Renal composite endpoint defined as: sustained confirmed $\geq 40\%$ decrease in eGFR to eGFR <60 mL/min/1.73 m² and/or end-stage kidney disease (dialysis ≥ 90 days or kidney transplantation, sustained confirmed eGFR < 15 mL/min/1.73 m²) and/or renal or cardiovascular death.

p-values are two-sided. p-values for the secondary endpoints and for single components are nominal. Time to first event was analysed in a Cox proportional hazards model. The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint. CI=confidence interval.

Nephropathy

Dapagliflozin reduced the incidence of events of the composite of confirmed sustained eGFR decrease, end-stage kidney disease, renal or cardiovascular death. The difference between groups was driven by reductions in events of the renal components; sustained eGFR decrease, end-stage kidney disease and renal death (Figure 2).

The hazard ratio for time to nephropathy (sustained eGFR decrease, end-stage kidney disease and renal death) was 0.53 (95% CI 0.43, 0.66) for dapagliflozin versus placebo.

In addition, dapagliflozin reduced the new onset of sustained albuminuria (hazard ratio 0.79 [95% CI 0.72, 0.87]) and led to greater regression of macroalbuminuria (hazard ratio 1.82 [95% CI 1.51, 2.20]) compared with placebo

Heart Failure with Reduced Ejection Fraction

Dapagliflozin And Prevention of Adverse outcomes in Heart Failure (DAPA-HF, NCT03036124) was an international, multicenter, randomized, double-blind, placebo-controlled study in patients with heart failure (New York Heart Association [NYHA] functional class II-IV) with reduced ejection fraction (left ventricular ejection fraction [LVEF] 40% or less) to determine whether FORXIGA reduces the risk of cardiovascular death and worsening heart failure.

Of 4744 patients, 2373 were randomized to FORXIGA 10 mg and 2371 to placebo and were followed for a median of 18 months. The mean age of the study population was 66 years, 77% were male and 70% were White, 5% Black or African-American, and 24% Asian.

At baseline, 68% patients were classified as NYHA class II, 32% class III, and 1% class IV; median LVEF was 32%. History of type 2 diabetes mellitus was present in 42%, and an additional 3% had type 2 diabetes mellitus based on a HbA1c $\geq 6.5\%$ at both enrollment and randomization.

At baseline, 94% of patients were treated with ACEi, ARB or angiotensin receptor-neprilysin inhibitor (ARNI, including sacubitril/valsartan 11%), 96% with beta-blocker, 71% with mineralocorticoid receptor antagonist (MRA), 93% with diuretic, and 26% had an implantable device.

FORXIGA reduced the incidence of the primary composite endpoint of CV death, hospitalization for heart failure or urgent heart failure visit (HR 0.74 [95% CI 0.65, 0.85]; p<0.0001). All three components of the primary composite endpoint individually contributed to the treatment effect. The FORXIGA and placebo event curves separated early and continued to diverge over the study period (Table 11, Figures 3A, 3B and 3C).

Table 11: Treatment Effect for the Primary Composite Endpoint*, its Components* and All-Cause Mortality in the DAPA-HF Study

Efficacy Variable (time to first occurrence)	Patients with events (event rate)		Hazard ratio (95% CI)	p-value†
	FORXIGA 10 mg N=2373	Placebo N=2371		
Composite of Hospitalization for Heart Failure, CV Death or Urgent Heart Failure Visit	386 (11.6)	502 (15.6)	0.74 (0.65, 0.85)	<0.0001
Composite of CV Death or Hospitalization for Heart Failure	382 (11.4)	495 (15.3)	0.75 (0.65, 0.85)	<0.0001
Components of the composite endpoints‡				
CV Death	227 (6.5)	273 (7.9)	0.82 (0.69, 0.98)	
Hospitalization for Heart Failure or Urgent Heart Failure Visit	237 (7.1)	326 (10.1)	0.70 (0.59, 0.83)	
Hospitalization for Heart Failure	231 (6.9)	318 (9.8)	0.70 (0.59, 0.83)	
Urgent Heart Failure Visit	10 (0.3)	23 (0.7)	0.43 (0.20, 0.90)	
All-Cause Mortality‡	276 (7.9)	329 (9.5)	0.83 (0.71, 0.97)	

N=Number of patients, CI=Confidence interval, CV=Cardiovascular.

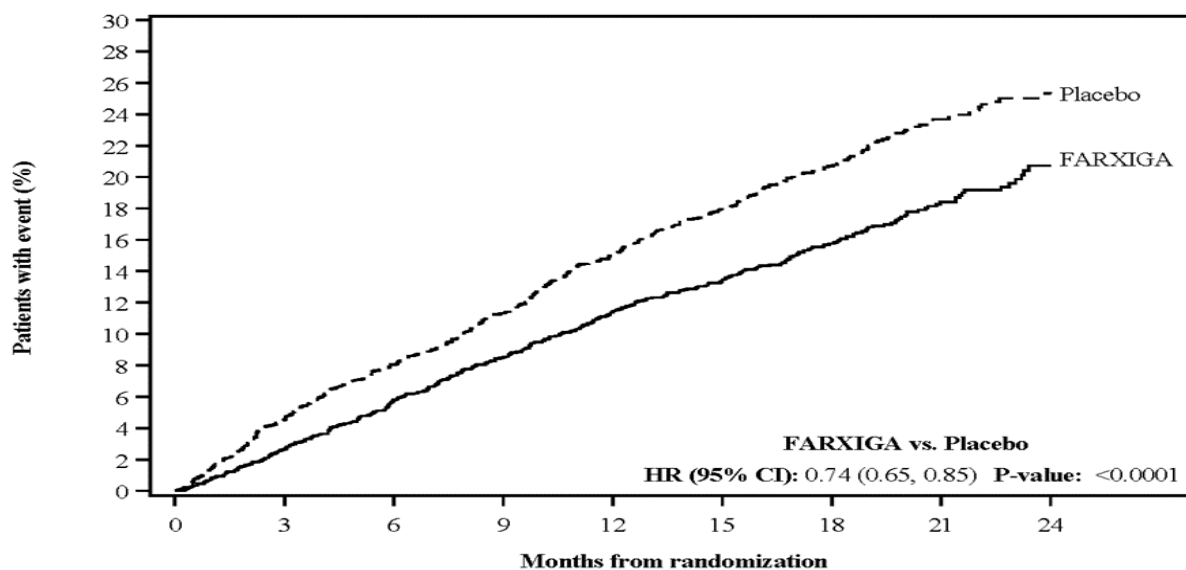
* Full analysis set.

† Two-sided p-values.

NOTE: Time to first event was analyzed in a Cox proportional hazards model. The number of first events for the single components are the actual number of first events for each component and does not add up to the number of events in the composite endpoint. Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

Figure 3: Kaplan-Meier Curves for the Primary Composite Endpoint (A), Cardiovascular Death (B), and Heart Failure Hospitalization (C) (DAPA-HF Study)

Figure 3A: Time to the First Occurrence of the Composite of Cardiovascular Death, Hospitalization for Heart Failure or Urgent Heart Failure Visit

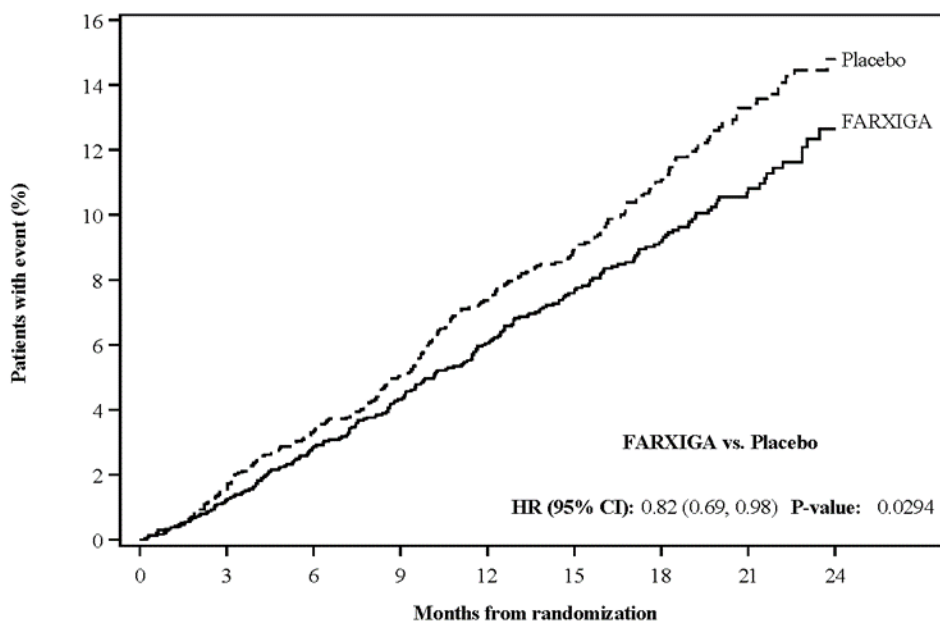


Patients at risk

FARXIGA:	2373	2305	2221	2147	2002	1560	1146	612	210
Placebo:	2371	2258	2163	2075	1917	1478	1096	593	210

NOTE: An urgent heart failure visit was defined as an urgent, unplanned, assessment by a physician, e.g. in an Emergency Department, and requiring treatment for worsening heart failure (other than just an increase in oral diuretics). Patients at risk is the number of patients at risk at the beginning of the period. HR=Hazard ratio, CI=Confidence interval.

Figure 3B: Time to the First Occurrence of Cardiovascular Death

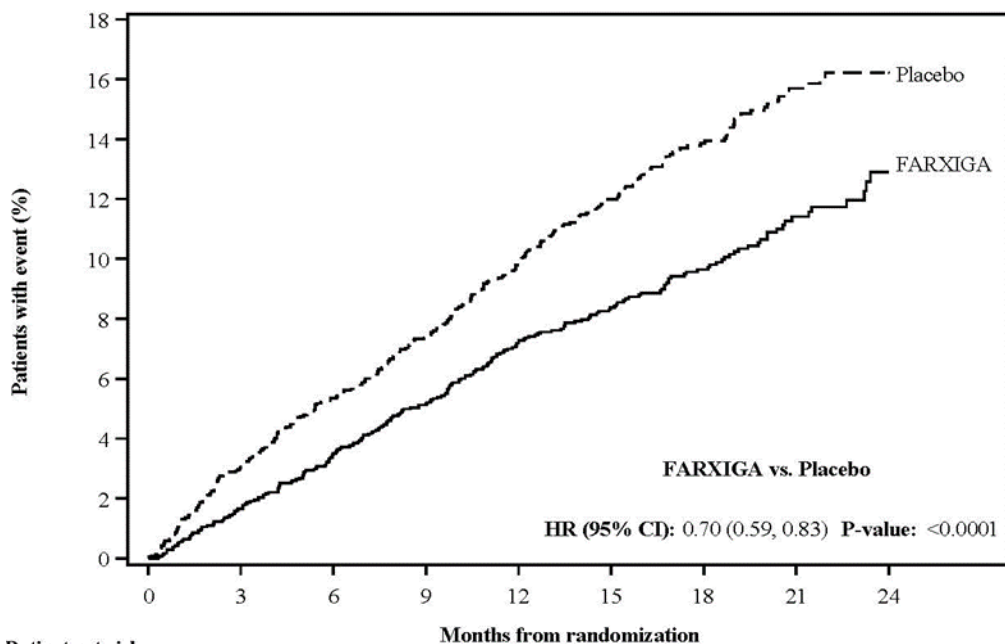


Patients at risk

FARXIGA:	2373	2339	2293	2248	2127	1664	1242	671	232
Placebo:	2371	2330	2279	2230	2091	1636	1219	664	234

Patients at risk is the number of patients at risk at the beginning of the period. HR=Hazard ratio, CI=Confidence interval.

Figure 3C: Time to the First Occurrence of Heart Failure Hospitalization



Patients at risk

	Months from randomization								
	0	3	6	9	12	15	18	21	24
FARXIGA:	2373	2306	2223	2153	2007	1563	1147	613	210
Placebo:	2371	2264	2168	2082	1924	1483	1101	596	212

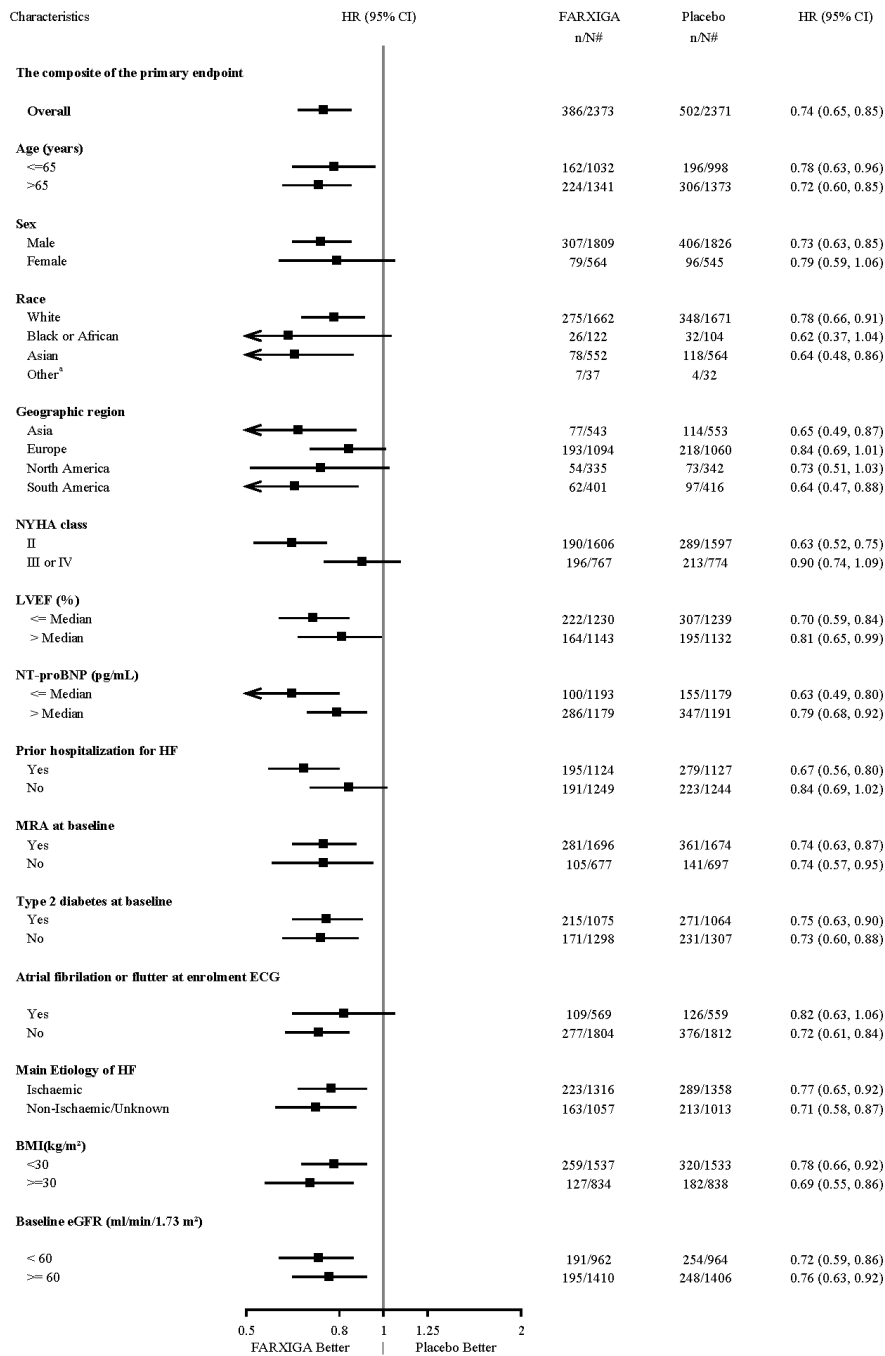
Patients at risk is the number of patients at risk at the beginning of the period.

HR=Hazard ratio, CI=Confidence interval.

FORXIGA reduced the total number of hospitalizations for heart failure (first and recurrent) events and CV death, with 567 and 742 total events in the FORXIGA-treated vs placebo group (Rate Ratio 0.75 [95% CI 0.65, 0.88]; p=0.0002).

The results of the primary composite endpoint were consistent across the subgroups examined, including heart failure patients with and without type 2 diabetes mellitus (Figure 7).

Figure 7: Treatment Effects for Primary Composite Endpoint (Cardiovascular Death and Heart Failure Events) Subgroup Analysis (DAPA-HF Study)



^a Hazard ratio estimates are not presented for subgroups with less than 15 events in total, both arms combined.

n/N# Number of subjects with event/number of subjects in the subgroup.

NT-proBNP = N-terminal pro b-type natriuretic peptide, HF = Heart failure, MRA = mineralocorticoid receptor antagonist, ECG = electrocardiogram, eGFR = estimated glomerular filtration rate.

Note: The figure above presents effects in various subgroups, all of which are baseline characteristics. The 95% confidence limits that are shown do not take into account the number of comparisons made and may not reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

Chronic Kidney Disease

The Study to Evaluate the Effect of Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease (DAPA-CKD, NCT03036150) was an international,

multicenter, randomized, double-blind, placebo-controlled study in patients with chronic kidney disease (CKD) (eGFR between 25 and 75 mL/min/1.73 m²) and albuminuria (urine albumin creatinine ratio [UACR] between 200 and 5000 mg/g) who were receiving standard of care background therapy, including a maximally tolerated, labeled daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). The trial excluded patients with autosomal dominant or autosomal recessive polycystic kidney disease, lupus nephritis, or ANCA-associated vasculitis and patients requiring cytotoxic, immunosuppressive, or immunomodulatory therapies in the preceding 6 months.

The primary objective was to determine whether FORXIGA reduces the incidence of the composite endpoint of $\geq 50\%$ sustained decline in eGFR, progression to end-stage kidney disease (ESKD) (defined as sustained eGFR < 15 mL/min/1.73 m², initiation of chronic dialysis treatment or renal transplant), CV or renal death.

A total of 4304 patients were randomized equally to FORXIGA 10 mg or placebo and were followed for a median of 28.5 months.

The mean age of the study population was 62 years and 67% were male. The population was 53% White, 4% Black or African-American, and 34% Asian; 25% were of Hispanic or Latino ethnicity. At baseline, mean eGFR was 43 mL/min/1.73 m², 44% of patients had an eGFR 30 mL/min/1.73 m² to less than 45 mL/min/1.73 m², and 15% of patients had an eGFR less than 30 mL/min/1.73 m². Median UACR was 950 mg/g. A total of 68% of the patients had type 2 diabetes mellitus at randomization. The most common etiologies of CKD were diabetic nephropathy (58%), ischemic/hypertensive nephropathy (16%), and IgA nephropathy (6%).

At baseline, 97% of patients were treated with ACEi or ARB. Approximately 44% were taking antiplatelet agents, and 65% were on a statin.

FORXIGA reduced the incidence of the primary composite endpoint of $\geq 50\%$ sustained decline in eGFR, progression to ESKD, CV or renal death (HR 0.61 [95% CI 0.51, 0.72]; $p < 0.0001$). The FORXIGA and placebo event curves separate by Month 4 and continue to diverge over the study period. The treatment effect reflected a reduction in $\geq 50\%$ sustained decline in eGFR, progression to ESKD, and CV death.

There were few renal deaths during the trial (Table 12, Figure 4).

FORXIGA also reduced the incidence of the composite endpoint of CV death or hospitalization for heart failure (HR 0.71 [95% CI 0.55, 0.92], $p = 0.0089$) and all-cause mortality (HR 0.69 [95% CI 0.53, 0.88], $p = 0.0035$).

Table 12: Treatment Effect for the Primary Composite Endpoint, its Components, and Secondary Composite Endpoints, in the DAPA-CKD Study

Efficacy Variable (time to first occurrence)	Patients with events (event rate)		Hazard ratio (95% CI)	p-value
	FORXIGA 10 mg N=2152	Placebo N=2152		
Composite of $\geq 50\%$ sustained eGFR decline, ESKD, CV or renal death	197 (4.6)	312 (7.5)	0.61 (0.51, 0.72)	<0.0001
$\geq 50\%$ sustained eGFR decline	112 (2.6)	201 (4.8)	0.53 (0.42, 0.67)	
ESKD*	109 (2.5)	161 (3.8)	0.64 (0.50, 0.82)	
CV Death	65 (1.4)	80 (1.7)	0.81 (0.58, 1.12)	
Renal Death	2 (<0.1)	6 (0.3)		
$\geq 50\%$ sustained eGFR decline, ESKD or renal death	142 (3.3)	243 (5.8)	0.56 (0.45, 0.68)	<0.0001

Table 12: Treatment Effect for the Primary Composite Endpoint, its Components, and Secondary Composite Endpoints, in the DAPA-CKD Study

Efficacy Variable (time to first occurrence)	Patients with events (event rate)		Hazard ratio (95% CI)	p-value
	FORXIGA 10 mg N=2152	Placebo N=2152		
CV death or Hospitalization for Heart Failure	100 (2.2)	138 (3.0)	0.71 (0.55, 0.92)	0.0089
Hospitalization for Heart Failure	37 (0.8)	71 (1.6)	0.51 (0.34, 0.76)	
All-Cause Mortality	101 (2.2)	146 (3.1)	0.69 (0.53, 0.88)	0.0035

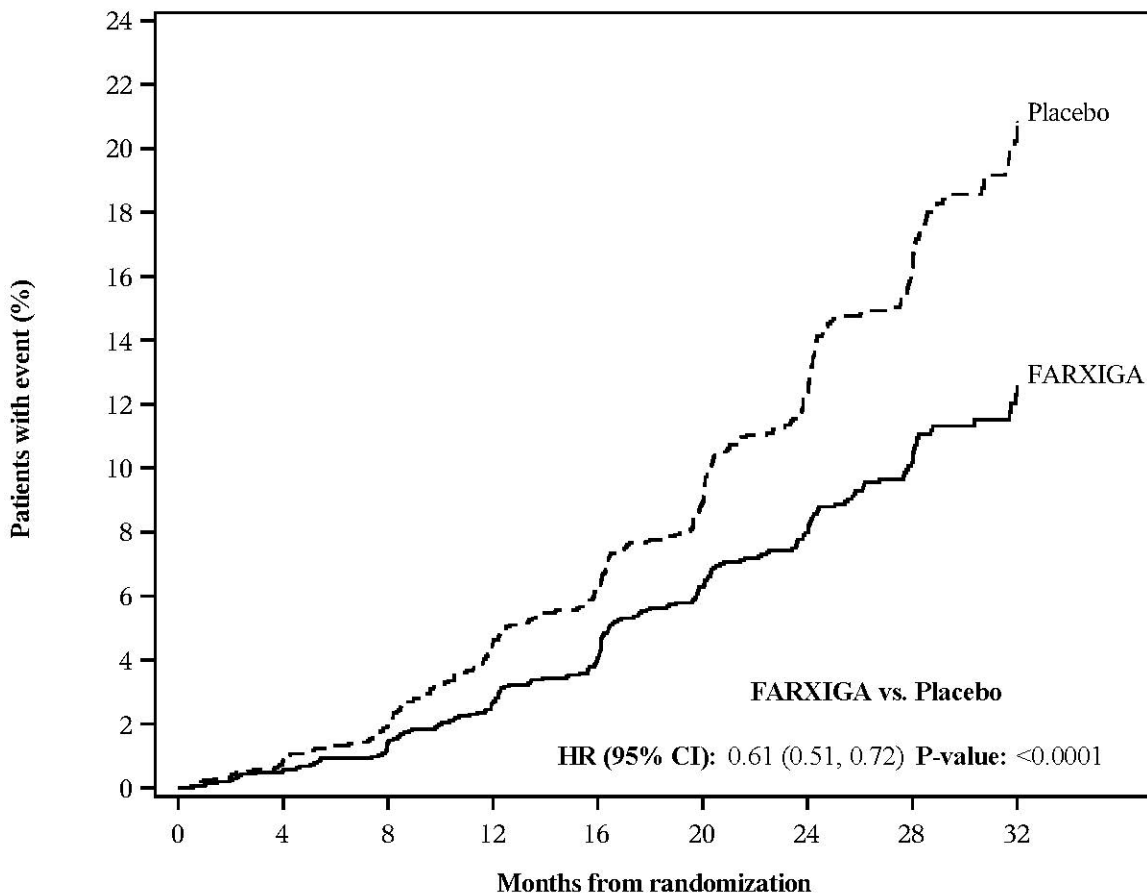
N=Number of patients, CI=Confidence interval, CV=Cardiovascular, ESKD=End stage kidney disease.

* ESKD is defined as sustained eGFR<15 mL/min/1.73 m², initiation of chronic dialysis treatment, or transplant.

NOTE: Time to first event was analyzed in a Cox proportional hazards model. Event rates are presented as the number of subjects with event per 100 patient years of follow-up.

There were too few events of renal death to compute a reliable hazard ratio.

Figure 4: Time to First Occurrence of the Primary Composite Endpoint, ≥50% Sustained Decline in eGFR, ESKD, CV or Renal Death (DAPA-CKD Study)



Patients at risk

FARXIGA:	2152	2001	1955	1898	1841	1701	1288	831	309
Placebo:	2152	1993	1936	1858	1791	1664	1232	774	270

Patients at risk is the number of subjects at risk at the beginning of the period. 1 month corresponds to 30 days. 2-sided p-value is displayed. HR, CI and p-value are from the Cox proportional hazard model. HR=hazard ratio; CI=confidence interval; eGFR=estimated glomerular filtration rate; ESKD=end stage kidney disease; CV=cardiovascular; vs=versus.

The results of the primary composite endpoint were consistent across the subgroups examined, including CKD patients with and without type 2 diabetes mellitus, causes of CKD, age, biological sex, race, UACR, and eGFR.

DAPA-CKD enrolled a population with relatively advanced CKD at high risk of progression. Exploratory analyses of a randomized, double-blind, placebo-controlled trial conducted to determine the effect of FORXIGA on CV outcomes (the DECLARE trial) support the conclusion that FORXIGA is also likely to be effective in patients with less advanced CKD.

5.2 Pharmacokinetic properties

Absorption

Dapagliflozin was rapidly and well absorbed after oral administration. Maximum dapagliflozin plasma concentrations (C_{max}) were usually attained within 2 hours after administration in the fasted state. Geometric mean steady-state dapagliflozin C_{max} and AUC values following once daily 10 mg doses of dapagliflozin were 158 ng/ml and 628 ngh/ml, respectively. The absolute oral bioavailability of dapagliflozin following the administration of a 10 mg dose is 78%. Administration with a high-fat meal decreased dapagliflozin C_{max} by up to 50% and prolonged T_{max} by approximately 1 hour but did not alter AUC as compared with the fasted state. These changes are not considered to be clinically meaningful. Hence, Forxiga can be administered with or without food.

Distribution

Dapagliflozin is approximately 91% protein bound. Protein binding was not altered in various disease states (e.g. renal or hepatic impairment). The mean steady-state volume of distribution of dapagliflozin was 118 l.

Biotransformation

Dapagliflozin is extensively metabolised, primarily to yield dapagliflozin 3-O-glucuronide, which is an inactive metabolite. Dapagliflozin 3-O-glucuronide or other metabolites do not contribute to the glucose-lowering effects. The formation of dapagliflozin 3-O-glucuronide is mediated by UGT1A9, an enzyme presents in the liver and kidney, and CYP-mediated metabolism was a minor clearance pathway in humans.

Elimination

The mean plasma terminal half-life (t_{1/2}) for dapagliflozin was 12.9 hours following a single oral dose of dapagliflozin 10 mg to healthy subjects. The mean total systemic clearance of dapagliflozin administered intravenously was 207 ml/min. Dapagliflozin and related metabolites are primarily eliminated via urinary excretion with less than 2% as unchanged dapagliflozin. After administration of a 50 mg [¹⁴C]-dapagliflozin dose, 96% was recovered, 75% in urine and 21% in feces. In feces, approximately 15% of the dose was excreted as parent drug.

Linearity

Dapagliflozin exposure increased proportional to the increment in dapagliflozin dose over the range of 0.1 to 500 mg and its pharmacokinetics did not change with time upon repeated daily dosing for up to 24 weeks.

Special populations

Renal impairment

At steady-state (20 mg once-daily dapagliflozin for 7 days), subjects with type 2 diabetes mellitus and mild, moderate or severe renal impairment (as determined by iohexol plasma clearance) had mean systemic exposures of dapagliflozin were 45%, 100% and 200% higher, respectively, than those of subjects with type 2 diabetes mellitus and normal renal function. There was no meaningful difference in exposure between patients with chronic kidney disease with and without type 2 diabetes.

Higher systemic exposure of dapagliflozin in patients with type 2 diabetes mellitus with renal impairment not result in a correspondingly higher 24-hour urinary glucose excretion.

The steady-state 24-hour urinary glucose excretion was highly dependent on renal function and 85, 52, 18 and 11 g of glucose/day was excreted by subjects with type 2 diabetes mellitus and normal renal function or mild, moderate or severe renal impairment, respectively. The impact of hemodialysis on dapagliflozin exposure is not known.

Hepatic impairment

In subjects with mild or moderate hepatic impairment (Child-Pugh classes A and B), mean C_{max} and AUC of dapagliflozin were up to 12% and 36% higher, respectively, compared to healthy matched control subjects. These differences were not considered to be clinically meaningful. In subjects with severe hepatic impairment (Child-Pugh class C) mean C_{max} and AUC of dapagliflozin were 40% and 67% higher than matched healthy controls, respectively.

Elderly (≥ 65 years)

There is no clinically meaningful increase in exposure based on age alone in subjects up to 70 years old. However, an increased exposure due to age-related decrease in renal function can be expected. There are insufficient data to draw conclusions regarding exposure in patients > 70 years old.

Paediatric population

Pharmacokinetics in the paediatric population have not been studied.

Gender

The mean dapagliflozin AUC_{ss} in females was estimated to be about 22% higher than in males.

Race

There were no clinically relevant differences in systemic exposures between White, Black or Asian races.

Body weight

Dapagliflozin exposure was found to decrease with increased weight. Consequently, low-weight patients may have somewhat increased exposure and patients with high weight somewhat decreased exposure. However, the differences in exposure were not considered clinically meaningful.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and fertility. Dapagliflozin did not induce tumours in either mice or rats at any of the doses evaluated in two-year carcinogenicity studies.

Reproductive and developmental toxicity

Direct administration of dapagliflozin to weanling juvenile rats and indirect exposure during late pregnancy (time periods corresponding to the second and third trimesters of pregnancy with respect to human renal maturation) and lactation are each associated with increased incidence and/or severity of renal pelvic and tubular dilatations in progeny.

In a juvenile toxicity study, when dapagliflozin was dosed directly to young rats from postnatal day 21 until postnatal day 90, renal pelvic and tubular dilatations were reported at all dose levels; pup exposures at the lowest dose tested were ≥ 15 times the maximum recommended human dose. These findings were associated with dose-related increases in kidney weight and macroscopic kidney enlargement observed at all doses. The renal pelvic and tubular dilatations observed in juvenile animals did not fully reverse within the approximate 1-month recovery period.

In a separate study of pre- and postnatal development, maternal rats were dosed from gestation day 6 through postnatal day 21, and pups were indirectly exposed *in utero* and throughout lactation. (A satellite study was conducted to assess dapagliflozin exposures in milk and pups.) Increased incidence or severity of renal pelvic dilatation was observed in adult offspring of treated dams, although only at the highest dose tested (associated maternal and pup dapagliflozin exposures were 1,415 times and 137 times, respectively, the human values at the maximum recommended human dose). Additional developmental toxicity was limited to dose-related reductions in pup body weights, and observed only at doses ≥ 15 mg/kg/day (associated with pup exposures that are ≥ 29 times the human values at the maximum recommended human dose). Maternal toxicity was evident only at the highest dose tested, and limited to transient reductions in body weight and food consumption at dose. The no observed adverse effect level (NOAEL) for developmental toxicity, the lowest dose tested, is associated with a maternal systemic exposure multiple that is approximately 19 times the human value at the maximum recommended human dose.

In additional studies of embryo-foetal development in rats and rabbits, dapagliflozin was administered for intervals coinciding with the major periods of organogenesis in each species. Neither maternal nor developmental toxicities were observed in rabbits at any dose tested; the highest dose tested is associated with a systemic exposure multiple of approximately 1,191 times the maximum recommended human dose. In rats, dapagliflozin was neither embryolethal nor teratogenic at exposures up to 1,441 times the maximum recommended human dose.

6. Pharmaceutical particulars

6.1 List of excipients

Tablet core

Microcrystalline cellulose (E460i)
Lactose, anhydrous
Crospovidone (E1201)
Silicon dioxide (E551)
Magnesium stearate (E470b)

Film-coating

Polyvinyl alcohol (E1203)
Titanium dioxide (E171)
Macrogol 3350
Talc (E553b)
Iron oxide yellow (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Alu/Alu blister

Pack sizes of 14, 28 and 98 film-coated tablets in non-perforated calendar blisters

Pack sizes of 30x1 and 90x1 film-coated tablets in perforated unit dose blisters

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

AstraZeneca (Israel) Ltd,

1 Atirei Yeda St.,

Kfar Saba 4464301.

8. Manufacturer and Legal Entity

AstraZeneca AB (PUBL), Sodertalje, Sweden.

Revised on Apr 2022